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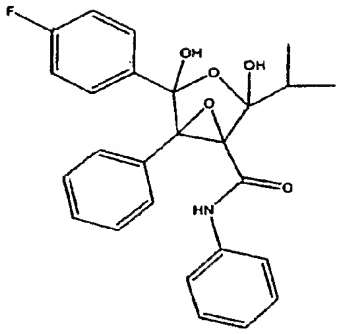
(54) **Title:** PROCESS FOR PREPARING FORMS OF ATORVASTATIN CALCIUM SUBSTANTIALLY FREE OF IMPURITIES



AED

(57) **Abstract:** The preparation of atorvastatin calcium epoxide dihydroxy (AED) is described. AED can be used as a standard or marker in determining the amount of AED in a sample. AED can therefore be used as a tool in preparing atorvastatin calcium substantially free of AED.

WO 2006/037125 A1

PROCESS FOR PREPARING FORMS OF ATORVASTATIN CALCIUM SUBSTANTIALLY FREE OF IMPURITIES

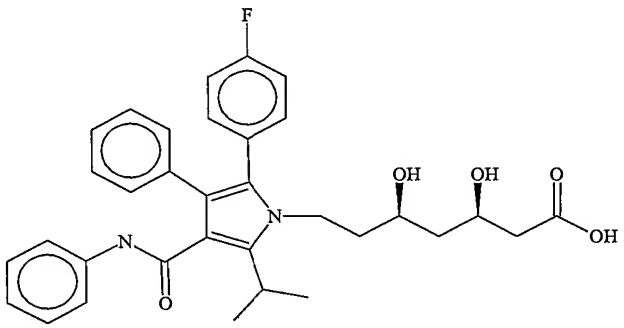
This application claims the benefit of U.S. Provisional Patent Application Ser. No. 60/613,687 filed September 28, 2004, which is incorporated herein by reference.

FIELD OF INVENTION

The present invention relates to atorvastatin calcium impurities and processes for preparing atorvastatin calcium substantially free of impurities.

BACKGROUND OF THE INVENTION

(βR, δR)-2-(4-fluorophenyl)-ß,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid ("atorvastatin") of formula (I)



$C_{33}H_{34}FN_2O_5$ Mw 558.64

Atorvastatin (I)

is well known in the art, and described, *inter alia*, in U.S. Patents Nos. 4,681,893, 5,273,995.

Atorvastatin calcium is a member of the class of drugs called statins. Statin drugs are said to be the most therapeutically effective drugs currently available for reducing low density lipoprotein (LDL) particle concentration in the blood stream of patients at risk for cardiovascular disease. A high level of LDL in the bloodstream has been linked to the formation of coronary lesions which obstruct the flow of blood and can rupture and promote thrombosis. Goodman and Gilman's *The Pharmacological Basis of Therapeutics* 879 (9th ed. 1996). Reducing plasma LDL levels has been shown to reduce the risk of clinical events in patients with cardiovascular disease and patients who are free of cardiovascular disease but who have hypercholesterolemia.

Scandinavian Simvastatin Survival Study Group, 1994; Lipid Research Clinics Program, 1984a, 1984b.

Atorvastatin calcium is marketed under the name LIPITOR® by Pfizer, Inc. Atorvastatin was first claimed in U.S. Patent No. 4,681,893. The hemi-calcium salt of atorvastatin is disclosed in U.S. Patent No. 5,273,995. Distinct crystalline forms are disclosed in several patents and patent applications. Crystalline Forms I, II, III and IV of atorvastatin calcium are the subjects of US Patent Nos. 5,959,156 and 6,121,461 assigned to Warner-Lambert and crystalline atorvastatin calcium Forms V and VIII are disclosed in commonly-owned published application nos. WO 01/36384 and US 2002/0183378, both of which are herein incorporated by reference.

Like any synthetic compound, atorvastatin hemi-calcium salts can contain extraneous compounds or impurities that can come from many sources. They can be unreacted starting materials, by-products of the reaction, products of side reactions, or degradation products. Impurities in atorvastatin hemi-calcium salts or any active pharmaceutical ingredient (API) are undesirable and, in extreme cases, might even be harmful to a patient being treated with a dosage form containing the API.

It is also known in the art that impurities in an API may arise from degradation of the API itself, which is related to the stability of the pure API during storage, and the manufacturing process, including the chemical synthesis. Process impurities include unreacted starting materials, chemical derivatives of impurities contained in starting materials, synthetic by-products, and degradation products.

In addition to stability, which is a factor in the shelf life of the API, the purity of the API produced in the commercial manufacturing process is clearly a necessary condition for commercialization. Impurities introduced during commercial manufacturing processes must be limited to very small amounts, and are preferably substantially absent. For example, the ICH Q7A guidance for API manufacturers requires that process impurities be maintained below set limits by specifying the quality of raw materials, controlling process parameters, such as temperature, pressure, time, and stoichiometric ratios, and including purification steps, such as crystallization, distillation, and liquid-liquid extraction, in the manufacturing process.

The product mixture of a chemical reaction is rarely a single compound with sufficient purity to comply with pharmaceutical standards. Side products and by-products of the reaction and adjunct reagents used in the reaction will, in most cases,

also be present in the product mixture. At certain stages during processing of an API, such as atorvastatin calcium, it must be analyzed for purity, typically, by HPLC or TLC analysis, to determine if it is suitable for continued processing and, ultimately, for use in a pharmaceutical product. The API need not be absolutely pure, as absolute purity is a theoretical ideal that is typically unattainable. Rather, purity standards are set with the intention of ensuring that an API is as free of impurities as possible, and, thus, is as safe as possible for clinical use. As discussed above, in the United States, the Food and Drug Administration guidelines recommend that the amounts of some impurities be limited to less than 0.1 percent.

Generally, side products, by-products, and adjunct reagents (collectively "impurities") are identified spectroscopically and/or with another physical method, and then associated with a peak position, such as that in a chromatogram, or a spot on a TLC plate. (Strobel p. 953, Strobel, H.A.; Heineman, W.R., Chemical Instrumentation: A Systematic Approach, 3rd dd. (Wiley & Sons: New York 1989)). Thereafter, the impurity can be identified, e.g., by its relative position in the chromatogram, where the position in a chromatogram is conventionally measured in minutes between injection of the sample on the column and elution of the particular component through the detector. The relative position in the chromatogram is known as the "retention time."

The retention time can vary about a mean value based upon the condition of the instrumentation, as well as many other factors. To mitigate the effects such variations have upon accurate identification of an impurity, practitioners use the "relative retention time" ("RRT") to identify impurities. (Strobel p. 922). The RRT of an impurity is its retention time divided by the retention time of a reference marker. It may be advantageous to select a compound other than the API that is added to, or present in, the mixture in an amount sufficiently large to be detectable and sufficiently low as not to saturate the column, and to use that compound as the reference marker for determination of the RRT.

Those skilled in the art of drug manufacturing research and development understand that a compound in a relatively pure state can be used as a "reference standard." A reference standard is similar to a reference marker, which is used for qualitative analysis only, but is used to quantify the amount of the compound of the reference standard in an unknown mixture, as well. A reference standard is an

"external standard," when a solution of a known concentration of the reference standard and an unknown mixture are analyzed using the same technique. (Strobel p. 924, Snyder p. 549, Snyder, L.R.; Kirkland, J.J. Introduction to Modern Liquid Chromatography, 2nd ed. (John Wiley & Sons: New York 1979)). The amount of the compound in the mixture can be determined by comparing the magnitude of the detector response. See also U.S. Patent No. 6,333,198, incorporated herein by reference.

The reference standard can also be used to quantify the amount of another compound in the mixture if a "response factor," which compensates for differences in the sensitivity of the detector to the two compounds, has been predetermined. (Strobel p. 894). For this purpose, the reference standard is added directly to the mixture, and is known as an "internal standard." (Strobel p. 925, Snyder p. 552).

The reference standard can serve as an internal standard when, without the deliberate addition of the reference standard, an unknown mixture contains a detectable amount of the reference standard compound using the technique known as "standard addition."

In a the "standard addition technique", at least two samples are prepared by adding known and differing amounts of the internal standard. (Strobel pp. 391-393, Snyder pp. 571, 572). The proportion of the detector response due to the reference standard present in the mixture without the addition can be determined by plotting the detector response against the amount of the reference standard added to each of the samples, and extrapolating the plot to zero concentration of the reference standard. (See, e.g., Strobel, Fig. 11.4 p. 392). The response of a detector in HPLC (e.g. UV detectors or refractive index detectors) can be and typically is different for each compound eluting from the HPLC column. Response factors, as known, account for this difference in the response signal of the detector to different compounds eluting from the column.

As is known by those skilled in the art, the management of process impurities is greatly enhanced by understanding their chemical structures and synthetic pathways, and by identifying the parameters that influence the amount of impurities in the final product.

Like any synthetic compound, atorvastatin calcium can contain extraneous compounds or impurities that can come from many sources. They can be unreacted

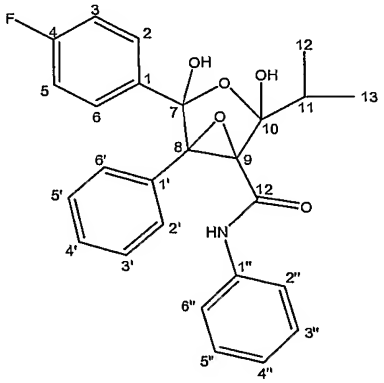
starting materials, by-products of the reaction, products of side reactions, or degradation products.

In this application the reference marker is the impurity N-formyl atorvastatin calcium in the API. Detection or quantification of the reference marker serves to establish the level of purity of the API. Use of a compound as a reference marker requires recourse to a sample of substantially pure compound.

Thus, there is a need in the art for a method for determining the level of impurities in atorvastatin calcium samples.

SUMMARY OF THE INVENTION

In one aspect the present invention provides the isolated atorvastatin calcium derivative – atorvastatin calcium epoxy dihydroxy (AED), having the formula:



$C_{26}H_{24}FNO_5$
Mol. Wt.: 449.47

The isolated AED of the present invention may be characterized by data selected from: ^{1}HNMR spectrum having hydrogen chemical shifts at about 1.20, 1.21, 2.37, 4.310, 6.032, 7.00, 7.06-7.29, 7.30, 7.39, 7.41, 7.56 ppm; a ^{13}CNMR spectrum having carbon chemical shifts at about 16.97, 34.66, 103.49, 106.66, 114.72, 120.59, 125.79, 128.21, 128.55, 128.74, 129.06, 129.57, 132.38, 132.51, 135.15, 161.61, 163.23 ppm ; an MS (ESI^+) spectrum having peaks at about having: m/z=472$(MNa)^+$, 454 $(MNa-H_2O)^+$, 432 $(MH-H_2O)^+$; 344 $(FPhCOC(Ph)=C-CONHPh)^+$ by retention time of about 32 min in HPLC analysis, such as the one described herein below, and by a relative retention time of about 1.88.

In another aspect, the present invention further provides a process for preparing AED comprising the steps of:

(a) combining atorvastatin calcium salt and a polar organic solvent or mixtures thereof with water, with methylene blue, to obtain a solution;

(b) irradiating the obtained solution for about 2 to about 10 hours;

(c) recovering AED.

Preferably, the irradiation of the solution of step (a) is performed in the presence of oxygen or air, in order to produce a photooxidation reaction. Therefore, the reaction is conducted, preferably, in an open vessel.

Preferably, the light source for irradiation is selected from the group consisting of a tungsten lamp, a UV lamp or sun light. More preferably, the light source for irradiation is a tungsten lamp. Moreover, when using a tungsten lamp as a light source, the yield is increased.

In yet another aspect, the present invention also provides a method for determining the level of AED in atorvastatin calcium comprising

(a) measuring by HPLC the area under a peak corresponding to AED in a reference standard comprising a known amount of AED;

(b) measuring by HPLC the area under a peak corresponding to AED in a sample comprising atorvastatin calcium and AED ;

(c) determining the amount of AED in the sample by comparing the area of step (a) to the area of step (b).

Unless otherwise specified, "atorvastatin calcium" may be either crude atorvastatin calcium or any form of atorvastatin, including, for example, crystalline Forms I, II, IV, V, VI, VII, VIII, IX, X, XI, XII and amorphous.

Preferably, the HPLC methodology used in the above method (for the use of AED as reference standard) includes the steps

(a) combining an atorvastatin calcium sample with a mixture of acetonitrile:tetrahydrofuran:water in a ratio of about 60:5:35, to obtain a solution;

(b) injecting the solution of step (a) into a 250X4.6 mm KR 100 5C-18 (or similar) column;

(c) eluting the sample from the column at about 50 min using a mixture of acetonitrile:tetrahydrofuran:buffer (31:9:60) and acetonitrile:buffer mix (75:25) as an eluent, and

(d) measuring the AED content in the relevant sample with a UV detector (preferably at a 254 nm wavelength).

In one aspect, the present invention provides an HPLC method for assaying atorvastatin calcium comprising the steps

(a) combining an atorvastatin calcium sample with a mixture of acetonitrile:tetrahydrofuran:water in a ratio of about 60:5:35, to obtain a solution;

(b) injecting the solution of step (a) into a 250X4.6 mm KR 100 5C-18 (or similar) column;

(c) eluting the sample from the column at about 50 min using a mixture of acetonitrile:tetrahydrofuran:buffer (31:9:60) and acetonitrile:buffer mix (75:25) as an eluent, and

(d) measuring the AED content in the relevant sample with a UV detector (preferably at a 254 nm wavelength).

Preferably, the buffer contains an aqueous solution of $NH_4H_2PO_4$ in a concentration of about 0.05M having a pH of about 5, and ammonium hydroxide. Preferably, the ratio of the aqueous solution of $NH_4H_2PO_4$ and ammonium hydroxide is of about 1 to 4, respectively.

Preferably, the buffer mix contains the above buffer and tetrahydrofuran. Preferably, the ratio of the above buffer and tetrahydrofuran is of about 1 to 6.67, respectively.

In another aspect, the present invention provides a process for preparing a form of atorvastatin calcium comprising less than about 0.10 w/w of, AED, by HPLC comprising the steps of

(a) obtaining one or more samples of one or more atorvastatin calcium batches;

(b) measuring the level of AED in each of the samples of (a);

(c) selecting the atorvastatin calcium batch that comprises a level of AED of less than about 0.10 w/w by HPLC, based on the measurement or measurements conducted in step (b); and

(d) using the batch selected in step (c) to prepare said any form of atorvastatin calcium.

Preferably, the atorvastatin calcium sample of step (a) comprises a sufficiently low level of AED. More preferably, the atorvastatin calcium sample of step (a) contains less than about 0.05 w/w by HPLC of AED.

Preferably, said any form of atorvastatin calcium refers to but is not limited to forms I, II, IV, V, VI, VII, VIII, IX, X, XI, XII and amorphous.

When the atorvastatin calcium sample of step (a) contains more than about 0.10 w/w by HPLC of AED, according to the measurement in step (b), the sample may be purified, prior to performing step (c).

Preferably, the atorvastatin calcium sample of step (a) obtained after purification, contains less than about 0.10 w/w by HPLC of AED, more preferably, of less than about 0.05 w/w by HPLC.

In yet another aspect, the present invention provides a method for reducing the level of AED in atorvastatin calcium sample by dissolving a selected form of atorvastatin calcium in an organic solvent, water or mixtures thereof, and crystallizing to obtain atorvastatin calcium having a reduced level of AED.

Preferably, the atorvastatin calcium sample obtained after purification contains less than about 0.10 w/w by HPLC of AED, more preferably, of less than about 0.05 w/w by HPLC.

Preferably, the selected form of atorvastatin calcium may be any form of atorvastatin, such as but not limited to form I, II, IV, V, VI, VII, VIII, IX, X, XI, XII and amorphous.

Preferably, when the selected form of atorvastatin calcium is the amorphous form, the crystallization is performed from either a mixture of ester and C_{5-10} cyclic or aliphatic hydrocarbon, from a polar aprotic organic solvent or from a mixture of a C_{6-10} aromatic hydrocarbon and a polar organic solvent, to give atorvastatin calcium amorphous form. Preferably, the ester is ethylacetate. A preferred C_{5-10} cyclic or aliphatic hydrocarbon is hexane. Preferably, the polar organic solvent is either a ketone or a nitrile. A preferred ketone is acetone. A preferred nitrile is acetonitrile. Preferably, the C_{6-10} aromatic hydrocarbon is toluene. A preferred polar organic solvent is tetrahydrofuran.

Preferably, when the selected form of atorvastatin calcium is form I, the crystallization is performed from a mixture of water miscible organic solvent and water, to give atorvastatin calcium form I. Preferably, the polar organic solvent is a

mixture of C_{1-4} alcohol and an ether. Preferably, the C_{1-4} alcohol is methanol. A preferred ether is methyltertbutylether.

Preferably, when the selected form of atorvastatin calcium is form II, the crystallization is performed from a mixture of water miscible organic solvent and water, to give atorvastatin calcium form II. Preferably, the water miscible organic solvent is a C_{1-4} alcohol. Preferably, the C_{1-4} alcohol is methanol.

Preferably, when the selected form of atorvastatin calcium is form IV, the crystallization is performed from a water miscible organic solvent, water and mixtures thereof, to give atorvastatin calcium form IV. Preferably, the water miscible organic solvent is a C_{1-4} alcohol. Preferably, the C_{1-4} alcohol is methanol, ethanol or 1-butanol. Preferably, when a mixture of a water miscible organic solvent and water is used, the water miscible organic solvent is ethanol.

Preferably, when the selected form of atorvastatin calcium is form V, the crystallization is performed from a mixture of water miscible organic solvent and water, to give atorvastatin calcium form V. Preferably, the water miscible organic solvent is a C_{1-4} alcohol. Preferably, the C_{1-4} alcohol is ethanol.

Preferably, when the selected form of atorvastatin calcium is form VI, the crystallization is performed from a mixture of polar aprotic organic solvent and water, to give atorvastatin calcium form VI. Preferably, the polar aprotic organic solvent is a ketone. Preferably, the ketone is acetone.

Preferably, when the selected form of atorvastatin calcium is form VII, the crystallization is performed from a C_{1-4} alcohol, to give atorvastatin calcium form VII. Preferably, the C_{1-4} alcohol is ethanol.

Preferably, when the selected form of atorvastatin calcium is form VIII, the crystallization is performed from a water miscible organic solvent, water and mixtures thereof, to give atorvastatin calcium form VIII. Preferably, the water miscible organic solvent is a C_{1-4} alcohol. Preferably, the C_{1-4} alcohol is ethanol, methanol, 1-butanol or iso-propanol.

Preferably, when the selected form of atorvastatin calcium is form IX, the crystallization is performed from a water miscible organic solvent, a C_{5-10} aliphatic hydrocarbon, water and mixtures thereof, to give atorvastatin calcium form IX. Preferably, the water miscible organic solvent is a C_{1-4} alcohol. Preferably, the C_{1-4} alcohol is ethanol, 1-butanol or iso-propanol. Preferably, the C_{5-10} aliphatic hydrocarbon is hexane.

Preferably, when the selected form of atorvastatin calcium is form X, the crystallization is performed from a mixture of a water miscible organic solvent and water, to give atorvastatin calcium form X. Preferably, the water miscible organic solvent is a C_{1-4} alcohol. Preferably, the C_{1-4} alcohol is ethanol.

Preferably, when the selected form of atorvastatin calcium is form XI, the crystallization is performed from a polar aprotic organic solvent or from a water miscible organic solvent, to give atorvastatin calcium form XI. Preferably, the polar aprotic organic solvent is a ketone. Preferably, the water miscible organic solvent is a C_{1-4} alcohol. Preferably, the ketone is methylethylketone. A preferred C_{1-4} alcohol is isopropanol.

Preferably, when the selected form of atorvastatin calcium is form XII, the crystallization is performed from a mixture of a water miscible organic solvent and water, to give atorvastatin calcium form XII. Preferably, the water miscible organic solvent is a C_{1-4} alcohol. A preferred C_{1-4} alcohol is ethanol.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: HPLC chromatogram of AED.

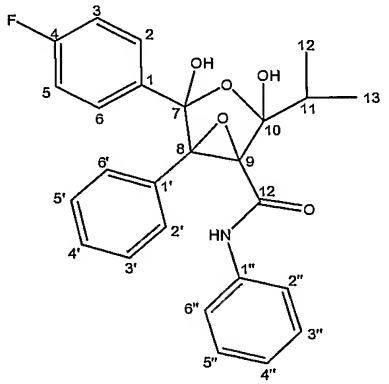
Figure 2: ^{1}HNMR spectrum of AED.

Figure 3: ^{13}CNMR spectrum of AED.

Figure 4: MS spectrum of AED.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides the isolated atorvastatin calcium derivative – atorvastatin calcium epoxy dihydroxy (AED), having the formula:



$C_{26}H_{24}FNO_5$
Mol. Wt.: 449.47

The isolated AED of the present invention may be characterized by data selected from: ^{1}HNMR spectrum having hydrogen chemical shifts at about 1.20, 1.21, 2.37, 4.310, 6.032, 7.00, 7.06-7.29, 7.30, 7.39, 7.41, 7.56 ppm; a ^{13}CNMR spectrum having carbon chemical shifts at about 16.97, 34.66, 103.49, 106.66, 114.72, 120.59, 125.79, 128.21, 128.55, 128.74, 129.06, 129.57, 132.38, 132.51, 135.15, 161.61, 163.23 ppm ; an MS (ESI^+) spectrum having peaks at about having: m/z=472$(MNa)^+$, 454 $(MNa-H_2O)^+$, 432 $(MH-H_2O)^+$; 344 $(FPhCOC(Ph)=C-CONHPh)^+$ by retention time of about 32 min in HPLC analysis, such as the one described herein below, and by a relative retention time of about 1.88.

The present invention further provides a process for preparing AED comprising the steps of:

(a) combining atorvastatin calcium salt and a polar organic solvent or mixtures thereof with water, with methylene blue, to obtain a solution;

(b) irradiating the obtained solution for about 2 to about 10 hours;

(c) recovering AED.

Preferably, the polar organic solvent is selected from the group consisting of C_{1-4} alcohol and nitrile. Preferably, the C_{1-4} alcohol is either methanol or ethanol. A preferred nitrile is acetonitrile. Preferably, a mixture of acetonitrile and water is used in step (a).

Preferably, the irradiation of the solution of step (a) is performed in the presence of oxygen or air, in order to produce a photooxidation reaction. Therefore, the reaction is conducted, preferably, in an open vessel.

Preferably, the light source for irradiation is selected from the group consisting of a tungsten lamp, a UV lamp or sun light. More preferably, the light source for irradiation is a tungsten lamp. Moreover, when using a tungsten lamp as a light source, the yield is increased.

Preferably, the solution of step (a) is irradiated for about 2 hours.

Preferably, the crude AED may recovered by evaporating the polar organic solvent or mixtures thereof with water, more preferably, under vacuum, followed by filtration and drying to obtain a precipitate, crude AED.

The recovered crude AED may be purified by a process of chromatography on a silica-gel column with an eluent of water immiscible polar organic solvent or a mixture of a polar organic solvent and a C_{5-8} aliphatic hydrocarbon. Preferably, the

water immiscible polar organic solvent is dichloromethane. A preferred polar organic solvent is ethyl acetate.

Preferably, AED may be further purified by a process of precipitation from a water immiscible polar organic solvent or from a mixture of a polar organic solvent and a C_{5-10} aliphatic hydrocarbon. Preferably, the water immiscible polar organic solvent is dichloromethane. A preferred polar organic solvent is ethyl acetate. Preferably, the C_{5-10} aliphatic hydrocarbon is hexane.

The present invention also provides a method for determining the level of AED in atorvastatin calcium comprising

(a) measuring by HPLC the area under a peak corresponding to AED in a reference standard comprising a known amount of AED;

(b) measuring by HPLC the area under a peak corresponding to AED in a sample comprising atorvastatin calcium and AED ;

(c) determining the amount of AED in the sample by comparing the area of step (a) to the area of step (b).

Unless otherwise specified, "atorvastatin calcium" may be either crude atorvastatin calcium or any form of atorvastatin, including, for example, crystalline Forms I, II, IV, V, VI, VII, VIII, IX, X, XI, XII and amorphous.

Preferably, the HPLC methodology used in the above method (for the use of AED as reference standard) includes the steps

(a) combining an atorvastatin calcium sample with a mixture of acetonitrile:tetrahydrofuran:water in a ratio of about 60:5:35, to obtain a solution;

(b) injecting the solution of step (a) into a 250X4.6 mm KR 100 5C-18 (or similar) column;

(c) eluting the sample from the column at about 50 min using a mixture of acetonitrile:tetrahydrofuran:buffer (31:9:60) and acetonitrile:buffer mix (75:25) as an eluent, and

(d) measuring the AED content in the relevant sample with a UV detector (preferably at a 254 nm wavelength).

The present invention further provides an HPLC method for assaying atorvastatin calcium comprising the steps

(a) combining an atorvastatin calcium sample with a mixture of acetonitrile:tetrahydrofuran:water in a ratio of about 60:5:35, to obtain a solution;

(b) injecting the solution of step (a) into a 250X4.6 mm KR 100 5C-18 (or similar) column;

(c) eluting the sample from the column at about 50 min using a mixture of acetonitrile:tetrahydrofuran:buffer (31:9:60) and acetonitrile:buffer mix (75:25) as an eluent, and

(d) measuring the AED content in the relevant sample with a UV detector (preferably at a 254 nm wavelength).

Preferably, the buffer contains an aqueous solution of $NH_4H_2PO_4$ in a concentration of about 0.05M having a pH of about 5, and ammonium hydroxide. Preferably, the ratio of the aqueous solution of $NH_4H_2PO_4$ and ammonium hydroxide is of about 1 to 4, respectively.

Preferably, the buffer mix contains the above buffer and tetrahydrofuran. Preferably, the ratio of the above buffer and tetrahydrofuran is of about 1 to 6.67, respectively.

The present invention provides a process for preparing a form of atorvastatin calcium comprising less than about 0.10 w/w of, AED,by HPLC comprising the steps of

(a) obtaining one or more samples of one or more atorvastatin calcium batches;

(b) measuring the level of AED in each of the samples of (a);

(c) selecting the atorvastatin calcium batch that comprises a level of AED of less than about 0.10 w/w by HPLC, based on the measurement or measurements conducted in step (b); and

(d) using the batch selected in step (c) to prepare said any form of atorvastatin calcium.

Preferably, the atorvastatin calcium sample of step (a) comprises a sufficiently low level of AED. More preferably, the atorvastatin calcium sample of step (a) contains less than about 0.05 w/w by HPLC of AED.

Preferably, said any form of atorvastatin calcium refers to but is not limited to forms I, II, IV, V, VI, VII, VIII, IX, X, XI, XII and amorphous.

When the atorvastatin calcium sample of step (a) contains more than about 0.10 w/w by HPLC of AED, according to the measurement in step (b), the sample may be purified, prior to performing step (c).

Preferably, the atorvastatin calcium sample of step (a) obtained after purification, contains less than about 0.10 w/w by HPLC of AED, more preferably, of less than about 0.05 w/w by HPLC.

The purification may be performed by crystallization from an organic solvent, water, or mixtures thereof.

The present invention also provides a method for reducing the level of AED in atorvastatin calcium sample by dissolving a selected form of atorvastatin calcium in an organic solvent, water or mixtures thereof, and crystallizing to obtain atorvastatin calcium having a reduced level of AED.

Preferably, the atorvastatin calcium sample obtained after purification contains less than about 0.10 w/w by HPLC of AED, more preferably, of less than about 0.05 w/w by HPLC.

Preferably, the selected form of atorvastatin calcium may be any form of atorvastatin, such as but not limited to form I, II, IV, V, VI, VII, VIII, IX, X, XI, XII and amorphous.

Preferably, when the selected form of atorvastatin calcium is the amorphous form, the crystallization is performed from either a mixture of ester and C_{5-10} cyclic or aliphatic hydrocarbon, from a polar aprotic organic solvent or from a mixture of a C_{6-10} aromatic hydrocarbon and a polar organic solvent, to give atorvastatin calcium amorphous form. Preferably, the ester is ethylacetate. A preferred C_{5-10} cyclic or aliphatic hydrocarbon is hexane. Preferably, the polar organic solvent is either a ketone or a nitrile. A preferred ketone is acetone. A preferred nitrile is acetonitrile. Preferably, the C_{6-10} aromatic hydrocarbon is toluene. A preferred polar organic solvent is tetrahydrofuran.

Preferably, when the selected form of atorvastatin calcium is form I, the crystallization is performed from a mixture of water miscible organic solvent and

water, to give atorvastatin calcium form I. Preferably, the polar organic solvent is a mixture of C_{1-4} alcohol and an ether. Preferably, the C_{1-4} alcohol is methanol. A preferred ether is methyltertbutylether.

Preferably, when the selected form of atorvastatin calcium is form II, the crystallization is performed from a mixture of water miscible organic solvent and water, to give atorvastatin calcium form II. Preferably, the water miscible organic solvent is a C_{1-4} alcohol. Preferably, the C_{1-4} alcohol is methanol.

Preferably, when the selected form of atorvastatin calcium is form IV, the crystallization is performed from a water miscible organic solvent, water and mixtures thereof, to give atorvastatin calcium form IV. Preferably, the water miscible organic solvent is a C_{1-4} alcohol. Preferably, the C_{1-4} alcohol is methanol, ethanol or 1-butanol. Preferably, when a mixture of a water miscible organic solvent and water is used, the water miscible organic solvent is ethanol.

Preferably, when the selected form of atorvastatin calcium is form V, the crystallization is performed from a mixture of water miscible organic solvent and water, to give atorvastatin calcium form V. Preferably, the water miscible organic solvent is a C_{1-4} alcohol. Preferably, the C_{1-4} alcohol is ethanol.

Preferably, when the selected form of atorvastatin calcium is form VI, the crystallization is performed from a mixture of polar aprotic organic solvent and water, to give atorvastatin calcium form VI. Preferably, the polar aprotic organic solvent is a ketone. Preferably, the ketone is acetone.

Preferably, when the selected form of atorvastatin calcium is form VII, the crystallization is performed from a C_{1-4} alcohol, to give atorvastatin calcium form VII. Preferably, the C_{1-4} alcohol is ethanol.

Preferably, when the selected form of atorvastatin calcium is form VIII, the crystallization is performed from a water miscible organic solvent, water and mixtures thereof, to give atorvastatin calcium form VIII. Preferably, the water miscible organic solvent is a C_{1-4} alcohol. Preferably, the C_{1-4} alcohol is ethanol, methanol, 1-butanol or iso-propanol.

Preferably, when the selected form of atorvastatin calcium is form IX, the crystallization is performed from a water miscible organic solvent, a C_{5-10} aliphatic hydrocarbon, water and mixtures thereof, to give atorvastatin calcium form IX. Preferably, the water miscible organic solvent is a C_{1-4} alcohol. Preferably, the C_{1-4}

alcohol is ethanol, 1-butanol or iso-propanol. Preferably, the C_{5-10} aliphatic hydrocarbon is hexane.

Preferably, when the selected form of atorvastatin calcium is form X, the crystallization is performed from a mixture of a water miscible organic solvent and water, to give atorvastatin calcium form X. Preferably, the water miscible organic solvent is a C_{1-4} alcohol. Preferably, the C_{1-4} alcohol is ethanol.

Preferably, when the selected form of atorvastatin calcium is form XI, the crystallization is performed from a polar aprotic organic solvent or from a water miscible organic solvent, to give atorvastatin calcium form XI. Preferably, the polar aprotic organic solvent is a ketone. Preferably, the water miscible organic solvent is a C_{1-4} alcohol. Preferably, the ketone is methylethylketone. A preferred C_{1-4} alcohol is isopropanol.

Preferably, when the selected form of atorvastatin calcium is form XII, the crystallization is performed from a mixture of a water miscible organic solvent and water, to give atorvastatin calcium form XII. Preferably, the water miscible organic solvent is a C_{1-4} alcohol. A preferred C_{1-4} alcohol is ethanol.

Optionally, the crystallization process may be repeated as necessary to obtain the desired atorvastatin calcium purity.

In order to preserve the purity level of atorvastatin calcium, the sample is maintained at a temperature of less than about 8°C, preferably the sample is maintained at a temperature of less than about 4°C.

Having described the invention with reference to certain preferred embodiments, other embodiments will become apparent to one skilled in the art from consideration of the specification. The invention is further defined by reference to the following examples describing in detail the preparation of the composition and methods of use of the invention. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the scope of the invention.

EXAMPLES

General

NMR analysis was done on Bruker DPX (300MHz for ^{1}HNMR, 150MHz for ^{13}CNMR), solvent $CDCl_3$.

Mass spectrometry was done on Micromass Q-TOS by method ESI^{+}

HPLC method

Column & Packing: Kromasil KR 100 5C-18 250x4.6mm is suitable.

Eluent A: Acetonitrile:Tetrahydrofuran:Buffer 31:9:60

Eluent B: Acetonitrile:Buffer Mix 75:25

Buffer solution: 0.05M aqueous $NH_4H_2PO_4$ adjusted to pH 5.0 with NH_4OH (diluted about 1:4)

Buffer Mix: A mixture of buffer solution and THF 60 volumes buffer and 9 volumes THF

Gradient conditions:

Time (minutes)	% Eluent A	% Eluent B	Flow rate
0	100	0	1.8
20	100	0	1.8
30	45	55	2.0
40	0	100	2.5
50	0	100	2.5

Detector: 254 nm

Diluent: 60:5:35 Acetonitrile:Tetrahydrofuran:water

Example 1: Atorvastatin epoxy dihydroxy synthesis

Atorvastatin calcium salt (1.0g) was dissolved in a mixture of acetonitrile-water (1200ml-800ml) and methylene blue (1mg) was added to the solution. The solution was stirred in an open flask at ambient temperature, and irradiated with visible light (tungsten lamp, 100W, distance 10cm) for 2 hours. Acetonitrile was evaporated under vacuum, and precipitated solid was filtered giving, after drying, a crude product (0.5g) containing impurities at 32 and 33 min. (HPLC control)

The crude product (3.6g) was purified by column chromatography on silica gel with dichloromethane as eluent, giving the mixture of the impurities at 32 and 33 min (1.6g). The product was dissolved in dichloromethane (15ml). The solution was stirred at ambient temperature while a solid was precipitated within a few minutes. The solid was filtered giving, after drying, the product (80mg).

Example 2: Crystallization of Form VIII

Atorvastatin hemi-calcium salt form V (5g) was added to a boiling solution of ethanol 96% (150ml) to obtain a solution. The solution was refluxed for 2 hours (during that time atorvastatin hemi-calcium salt was recrystallized), then cooled to 20°C during 1.5 hours and stirred at this temperature for an additional 16 hours. Filtration and drying in a vacuum oven at 40°C for 24 hours and then at 60°C for 24 hours gave atorvastatin hemi-calcium salt form VIII.

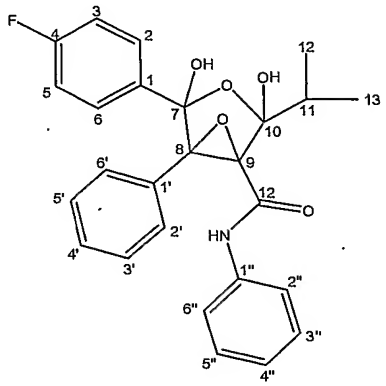
Example 3: Crystallization of the forms of atorvastatin calcium

Modifying the process in Example 2 by changing the medium of crystallization results in the following crystal forms:

Crystal form	Medium of crystallization
Amorphous	Ethyl acetate/n-Hexane (Esters/aliphatic or cyclic or branched Hydrocarbons)
Amorphous	Acetone Acetonitrile
Amorphous	THF/Toluene
Form I	traces of MTBE/MeOH/water
Form II	MeOH/water
Form IV	1-Butanol EtOH/water MeOH
Form V	EtOH/water
Form VI	Acetone/water
Form VII	EtOH
Form VIII	EtOH, MeOH/water EtOH 1-Butanol/water IPA/water
Form IX	1-Butanol 1-Butanol/n-Hexane 1-Butanol/IPA 1-Butanol/water EtOH 1-Butanol/EtOH
Form X	EtOH/water
Form XI	MEK IPA
Form XII	EtOH/water

What is claimed is:

1. Isolated atorvastatin epoxy dihydroxy (AED), having the formula:



2. The isolated AED of claim 1, characterized by data selected from the group consisting of: ^{1}HNMR spectrum having hydrogen chemical shifts at about 1.20, 1.21, 2.37, 4.31, 6.032, 7, 7.06-7.29, 7.3, 7.39, 7.41 and 7.56 ppm; ^{13}CNMR spectrum having carbon chemical shifts at about 16.97, 34.66, 103.49, 106.66, 114.72, 120.59, 125.79, 128.21, 128.55, 128.74, 129.06, 129.57, 132.38, 132.51, 135.15, 161.61and 163.23 ppm; and by a MS (ESI^{+}) spectrum having peaks at about: m/z=472$(MNa)^{+}$, 454 $(MNa\text{-}H_2O)^{+}$, 432 $(MH\text{-}H_2O)^{+}$; 344 $(FPhCOC(Ph)=C\text{-}CONHPh)^{+}$.

3. The AED of claim 2, characterized by a ^{13}HNMR spectrum depicted in figure 2.

4. The AED of claim 2, characterized by a ^{13}CNMR spectrum depicted in figure 3.

5. The AED of claim 2, characterized by a MS spectrum depicted in figure 4.

6. A process for the preparation of AED of claim 1, comprising the steps of:

(a) combining atorvastatin calcium salt and a polar organic solvent or mixtures thereof with water, with methylene blue, to obtain a solution;

(b) irradiating the obtained solution for about 2 to about 10 hours;

(c) recovering AED.

7. The process of claim 6, wherein the organic solvent is selected from the group consisting of a C_{1-4} alcohol and nitrile.
8. The process of claim 7, wherein the C_{1-4} alcohol is either methanol or ethanol.
9. The process of claim 7, wherein the nitrile is acetonitrile.
10. The process of claim 6, wherein a mixture of acetonitrile and water is used in step (a).
11. The process of claim 6, wherein the irradiation of the solution in step (a) is performed in the presence of oxygen or air.
12. The process of claim 6, the light source for irradiation is selected from the group consisting of a tungsten lamp, a UV lamp or sun light.
13. The process of claim 12, wherein the light source for irradiation is a tungsten lamp.
14. The process of claim 6, wherein the recovered crude AED is purified by chromatography on a silica gel column.
15. The process of claim 14, wherein the eluent is selected from the group consisting of a water immiscible polar organic solvent as and a mixture of a polar organic solvent and a C_{5-8} aliphatic hydrocarbon.
16. The process of claim 15, wherein the water immiscible polar organic solvent is dichloromethane.
17. The process of claim 15, wherein the polar organic solvent is ethylacetate.
18. The process of claim 15, wherein the C_{5-8} aliphatic hydrocarbon is hexane.
19. The process of claim 6, wherein the purified crude AED is further purified by a process of precipitation from a water immiscible polar organic solvent or from a mixture of a polar organic solvent and a C_{5-10} aliphatic hydrocarbon.
20. The process of claim 19, wherein the water immiscible polar organic solvent is dichloromethane.
21. The process of claim 19, wherein the polar organic solvent is ethyl acetate.
22. The process of claim 19, wherein the C_{5-10} aliphatic hydrocarbon is hexane.
23. AED prepared according to any of claims 6 to 22.
24. A method for determining the level of AED in atorvastatin calcium comprising

(b) measuring by HPLC the area under a peak corresponding to AED in a reference standard comprising a known amount of AED;

(c) measuring by HPLC the area under a peak corresponding to AED in a sample comprising atorvastatin calcium and AED;

(d) determining the amount of AED in the sample by comparing the area of step (a) to the area of step (b).

25. The method of claim 24, wherein atorvastatin calcium is either crude atorvastatin calcium or any form of atorvastatin calcium.

26. The method of claim 25, wherein said from atorvastatin calcium is selected from the group consisting of form I, II, IV, V, VI, VII, VIII, IX, X, XI, XII, and amorphous.

27. The method of claim 24, wherein the measuring by HPLC in step (a), step (b), or both, includes the following:

(a) combining an atorvastatin calcium sample with a mixture of acetonitrile:tetrahydrofuran:water in a ratio of about 60:5:35, to obtain a solution;

(b) injecting the solution of step (a) into a 250X4.6 mm KR 100 5C-18 (or similar) column;

(c) eluting the standard or sample from the column at about 50 min using a mixture of acetonitrile:tetrahydrofuran:buffer (31:9:60) and acetonitrile:buffer mix (75:25) as an eluent, and

(d) measuring the AED content in the standard or sample with a UV detector.

28. The method of claim 27, wherein the UV wavelength is about 254 nm.

29. An HPLC method for assaying atorvastatin calcium comprising the steps of

(a) combining an atorvastatin calcium sample with a mixture of acetonitrile:tetrahydrofuran:water in a ratio of about 60:5:35, to obtain a solution;

(b) injecting the solution of step (a) into a 250X4.6 mm KR 100 5C-18 (or similar) column;

(c) eluting the standard or sample from the column at about 50 min using a mixture of acetonitrile:tetrahydrofuran:buffer (31:9:60) and acetonitrile:buffer mix (75:25) as an eluent, and

(d) measuring the AED content in the standard or sample with a UV detector.

30. The method of claim 29, wherein the UV wavelength is about 254 nm.

31. The method of claim 29, wherein the buffer contains an aqueous solution of $NaHPO_4$ in a concentration of about 0.05M having a pH of about 5, and ammonium hydroxide.

32. The method of claim 31, wherein the ratio of the said aqueous solution of $NaHPO_4$ and the ammonium hydroxide is of about 1 to 4, respectively.

33. The method of claim 29, wherein the buffer mix contains the buffer of claim 31 and tetrahydrofuran.

34. The method of claim 33, wherein the ratio of the said buffer of claim 31 and tetrahydrofuran is of about 1 to 6.67, respectively.

35. A process for preparing a form of atorvastatin calcium comprising less than about 0.10 w/w of AED, by HPLC comprising the steps of

(a) obtaining one or more samples of one or more atorvastatin calcium batches;

(b) measuring the level of AED in each of the samples of (a);

(c) selecting the atorvastatin calcium batch that comprises a level of AED of less than a about 0.10 w/w by HPLC, based on the measurement or measurements conducted in step (b); and

(d) using the batch selected in step (c) to prepare said any form of atorvastatin calcium.

36. The process of claim 35, wherein the atorvastatin calcium sample of step (a) contains less than about 0.05 w/w by HPLC of AED.

37. The process of claim 35, wherein said any form of atorvastatin calcium is selected form the group consisting of form I, II, IV, V, VI, VII, VIII, IX, X, XI, XII, and amorphous.

38. The process of claim 35, wherein, if the atorvastatin calcium sample in step (a) contains more than about 0.10 w/w by HPLC of AED, the sample may be purified, prior to performing step (c).
39. The process of claim 35, wherein the atorvastatin calcium of step (a) obtained after purification, contains less than about 0.10 w/w by HPLC of AED.
40. The process of claim 39, wherein the atorvastatin calcium of step (a) obtained after purification, contains less than about 0.05 w/w by HPLC of AED.
41. The process of claim 35, wherein the purification is done by crystallization from an organic solvent, water, or mixtures thereof.
42. A method for reducing the level of AED in atorvastatin calcium sample by dissolving a selected form of atorvastatin calcium in an organic solvent, water or mixtures thereof, and crystallizing to obtain atorvastatin calcium having a reduced level of AED.
43. The method of claim 42, wherein the atorvastatin calcium obtained after purification, contains less than about 0.10 w/w by HPLC of AED.
44. The process of claim 43, wherein the atorvastatin calcium obtained after purification, contains less than about 0.05 w/w by HPLC of AED.
45. The method of claim 42, wherein the selected form of atorvastatin calcium is selected from group consisting of form I, II, IV, V, VI, VII, VIII, IX, X, XI, XII, and amorphous.
46. The method of claim 42, wherein the selected form of atorvastatin calcium is amorphous, the crystallization is performed from a mixture of ester and C_{5-10} cyclic or aliphatic hydrocarbon.
47. The method of claim 46, wherein the ester is ethylacetate.
48. The method of claim 46, wherein the C_{5-10} cyclic or aliphatic hydrocarbon is hexane.
49. The method of claim 42, wherein the selected form of atorvastatin calcium is amorphous, the crystallization is performed from a polar aprotic organic solvent.
50. The method of claim 49, wherein the polar organic solvent is either a ketone or a nitrile.

51. The method of claim 50, wherein the ketone is acetone.
52. The method of claim 50, wherein the nitrile is acetonitrile.
53. The method of claim 42, wherein the selected form of atorvastatin calcium is amorphous, the crystallization is performed from a mixture of a C_{6-10} aromatic hydrocarbon and a polar organic solvent.
54. The method of claim 53, wherein the C_{6-10} aromatic hydrocarbon is toluene.
55. The method of claim 53, wherein the polar organic solvent is tetrahydrofuran.
56. The method of any of the claims 47 to 54, wherein the obtained atorvastatin calcium is amorphous.
57. The method of claim 42, wherein the selected form of atorvastatin calcium is form I, the crystallization is performed from a mixture of a polar organic solvent and water.
58. The method of claim 58, wherein the polar organic solvent is a mixture of C_{1-4} alcohol and an ether.
59. The method of claim 58, wherein the C_{1-4} alcohol methanol.
60. The method of claim 58, wherein the ether is methyltertbutylether.
61. The method of claim 57, wherein the obtained atorvastatin calcium is form I.
62. The method of claim 42, wherein the selected form of atorvastatin calcium is form II, the crystallization is performed from a mixture of water miscible organic solvent and water.
63. The method of claim 62, wherein the water miscible organic solvent is a C_{1-4} alcohol.
64. The method of claim 63, wherein the C_{1-4} alcohol is methanol.
65. The method of claim 62, wherein the obtained atorvastatin calcium is form II.
66. The method of claim 42, wherein the selected form of atorvastatin calcium is form IV, the crystallization is performed from a water miscible organic solvent, water and mixtures thereof.
67. The method of claim 66, wherein the water miscible organic solvent is a C_{1-4} alcohol.

68. The method of claim 67, wherein the C_{1-4} alcohol is methanol, ethanol or 1-butanol.
69. The method of claim 66, wherein a mixture of a water miscible organic solvent and water is used.
70. The method of claim 69, wherein the water miscible organic solvent is ethanol.
71. The method of claim 66, wherein the obtained atorvastatin calcium is form IV.
72. The method of claim 42, wherein the selected form of atorvastatin calcium is form V, the crystallization is performed from a mixture of water miscible organic solvent and water.
73. The method of claim 72, wherein the water miscible organic solvent is a C_{1-4} alcohol.
74. The method of claim 73, wherein the C_{1-4} alcohol is ethanol.
75. The method of claim 72, wherein the obtained atorvastatin calcium is form V.
76. The method of claim 42, wherein the selected form of atorvastatin calcium is form VI, the crystallization is performed from a mixture of polar aprotic organic solvent and water.
77. The method of claim 76, wherein the polar aprotic organic solvent is a ketone.
78. The method of claim 77, wherein the the ketone is acetone.
79. The method of claim 76, wherein the obtained atorvastatin calcium is form VI.
80. The method of claim 42, wherein the selected form of atorvastatin calcium is form VII, the crystallization is performed from a C_{1-4} alcohol.
81. The method of claim 80, wherein the C_{1-4} alcohol is ethanol.
82. The method of claim 70, wherein the obtained atorvastatin calcium is form VII.
83. The method of claim 42, wherein the selected form of atorvastatin calcium is form VIII, the crystallization is performed from a water miscible organic solvent, water and mixtures thereof.
84. The method of claim 83, wherein the water miscible organic solvent is a C_{1-4} alcohol.

85. The method of claim 84, wherein the C_{1-4} alcohol is ethanol, methanol, 1-butanol or iso-propanol.
86. The method of claim 83, wherein the obtained atorvastatin calcium is form VIII.
87. The method of claim 42, wherein the selected form of atorvastatin calcium is form IX, the crystallization is performed from a water miscible organic solvent, a C_{5-10} aliphatic hydrocarbon, water and mixtures thereof.
88. The method of claim 87, wherein the water miscible organic solvent is a C_{1-4} alcohol.
89. The method of claim 87, wherein the C_{1-4} alcohol is ethanol, 1-butanol or iso-propanol.
90. The method of claim 87, wherein the C_{5-10} aliphatic hydrocarbon is hexane.
91. The method of claim 87, wherein the obtained atorvastatin calcium is form IX.
92. The method of claim 42, wherein the selected form of atorvastatin calcium is form X, the crystallization is performed from a mixture of a water miscible organic solvent and water.
93. The method of claim 92, wherein the water miscible organic solvent is a C_{1-4} alcohol.
94. The method of claim 93, wherein the the C_{1-4} alcohol is ethanol.
95. The method of claim 92, wherein the obtained atorvastatin calcium is form X.
96. The method of claim 42, wherein the selected form of atorvastatin calcium is form XI, the crystallization is performed from a polar aprotic organic solvent.
97. The method of claim 96, wherein polar aprotic organic solvent is a ketone.
98. The method of claim 96, wherein the ketone is methylethylketone.
99. The method of claim 96, wherein the selected form of atorvastatin calcium is form XI, the crystallization is performed from a water miscible organic solvent.
100. The method of claim 99, wherein the water miscible organic solvent is a C_{1-4} alcohol.

101. The method of claim 100, wherein the preferred C_{1-4} alcohol is isopropanol.

102. The method of any of the claims 96 to 101, wherein the obtained atorvastatin calcium is form XI.

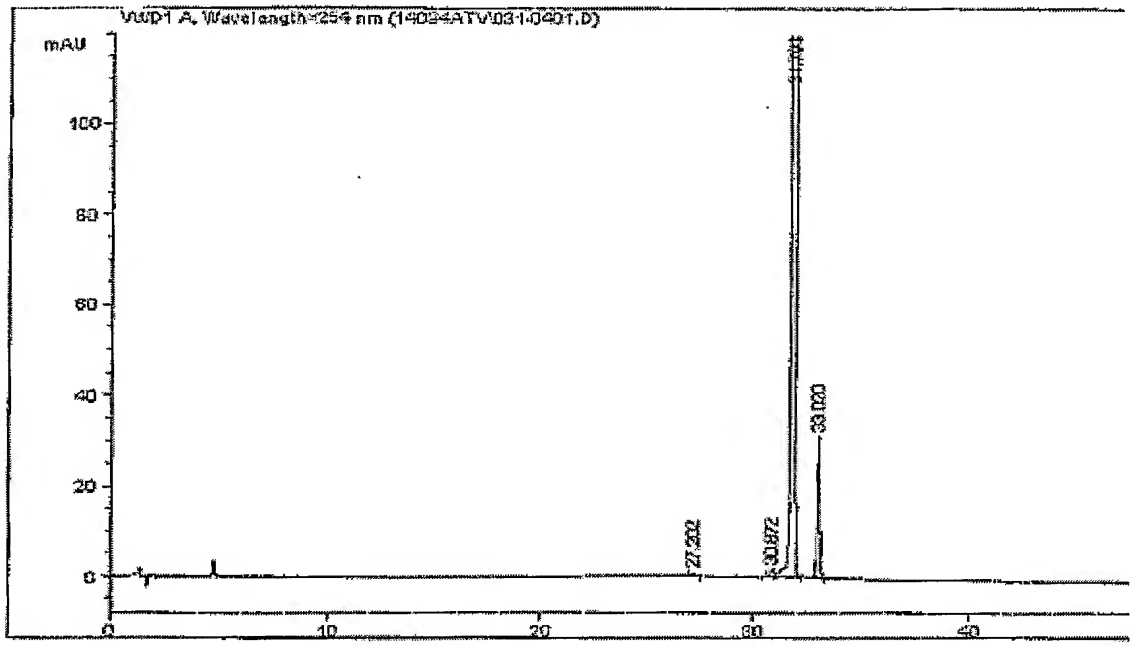
103. The method of claim 42, wherein the selected form of atorvastatin calcium is form XII, the crystallization is performed from a mixture of a water miscible organic solvent and water.

104. The method of claim 103, wherein the water miscible organic solvent is a C_{1-4} alcohol.

105. The method of claim 104, wherein the C_{1-4} alcohol is ethanol.

106. The method of claims 103, wherein the obtained atorvastatin calcium is form XII.

FIGURE 1



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

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1	27.202	BB	0.1567	6.19843	6.23778e-1	0.0858
2	30.872	BV	0.1709	17.34458	1.47264	0.2400
3	31.791	VB	0.1235	6949.49316	872.40076	96.1521
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Totals :				7227.60493	905.51001	

FIGURE 2

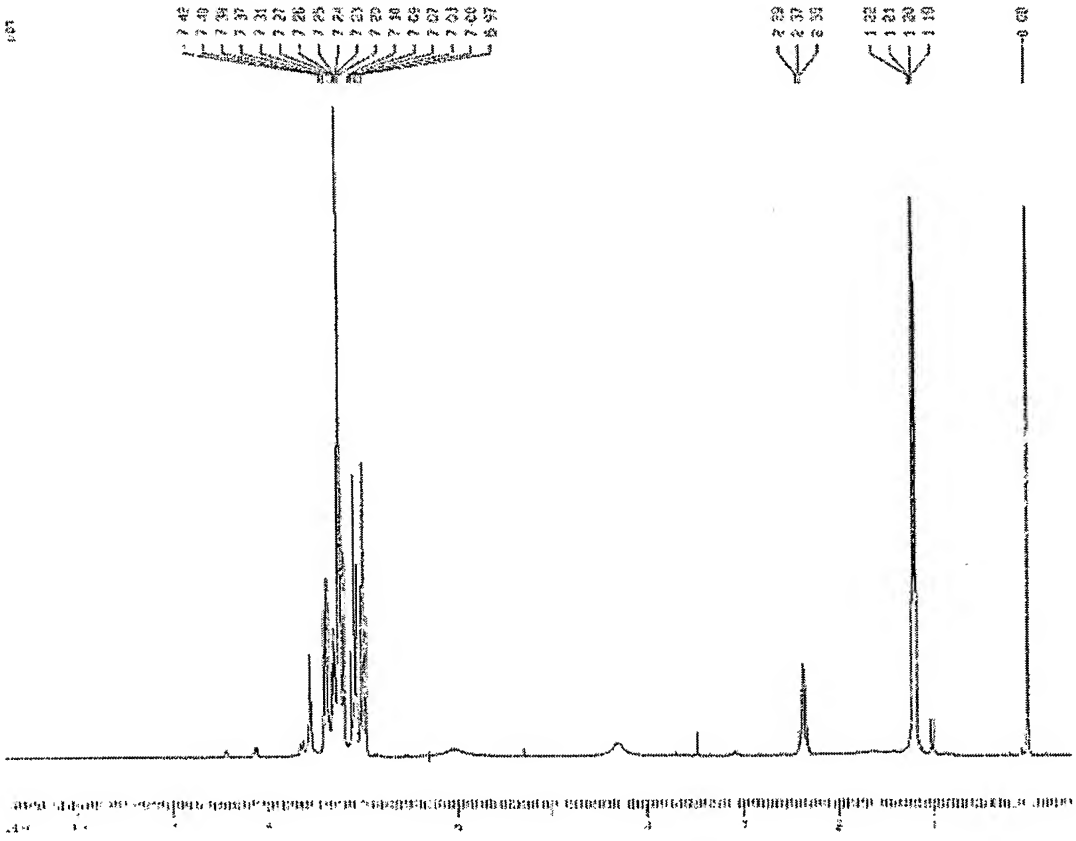


FIGURE 3

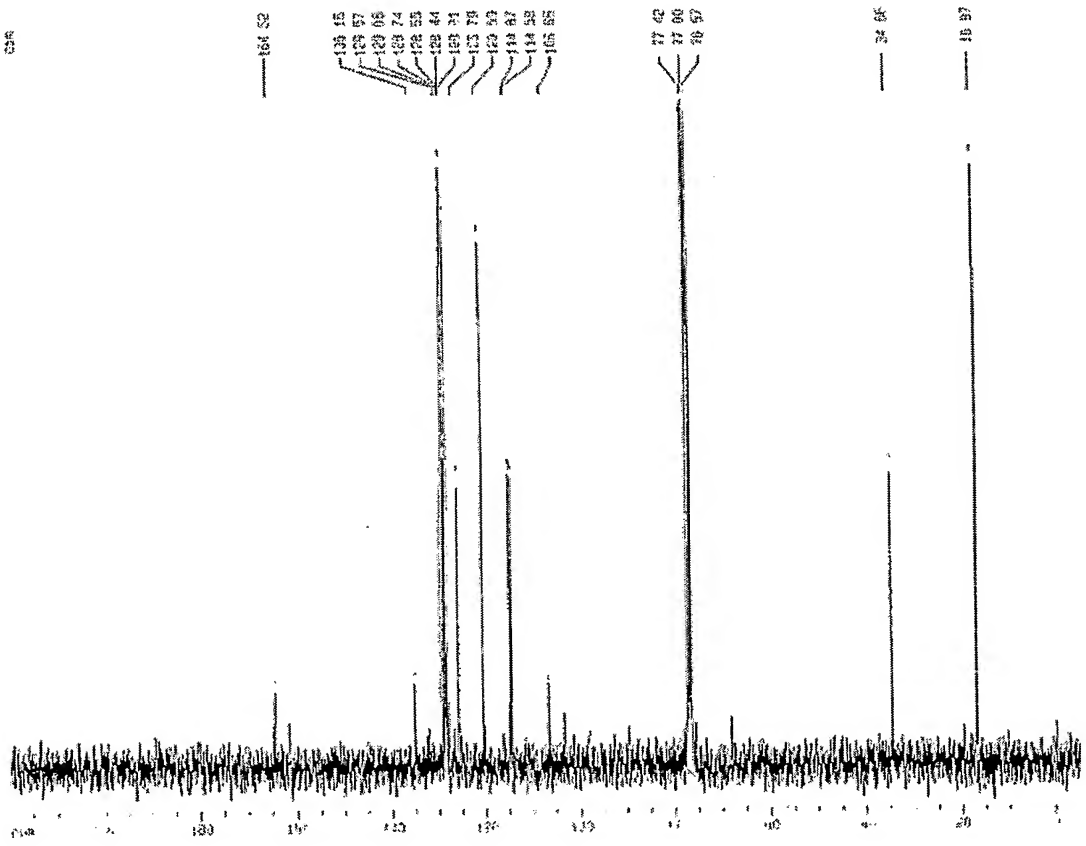
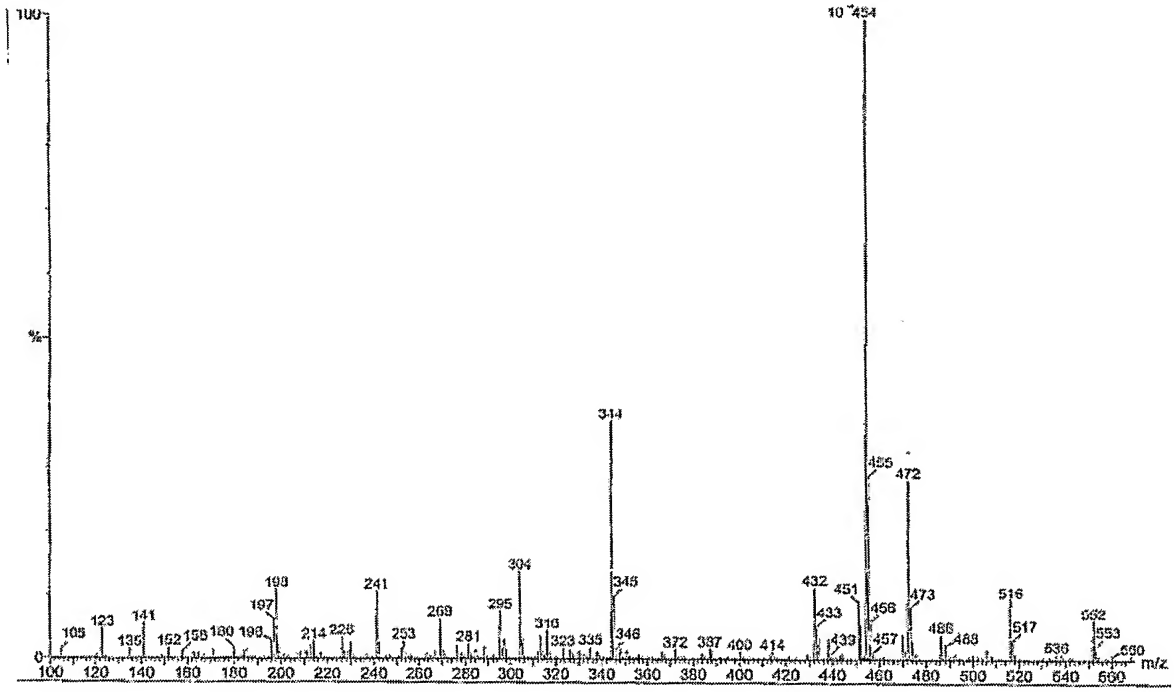


FIGURE 4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100 120 140 160 180 200 220 240 260 280 300 320 340 360 380 400 420 440 460 480 500 520 540 560 m/z

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/035159

A. CLASSIFICATION OF SUBJECT MATTER
C07D493/04 C07D207/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 121 461 A (MCKENZIE A T) 19 September 2000 (2000-09-19) cited in the application the whole document	42-106
X	WO 2004/050618 A (TEVA PHARMACEUTICAL INDUSTRIES LTD. ET AL) 17 June 2004 (2004-06-17) the whole document	42-106
X	EP 1 424 324 A (TEVA PHARMACEUTICAL INDUSTRIES LIMITED) 2 June 2004 (2004-06-02) the whole document	42-106
X	WO 01/28999 A (EGIS GYOGYSZERGYAR RT.) 26 April 2001 (2001-04-26) the whole document	42-106

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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Date of the actual completion of the international search	Date of mailing of the international search report
20 January 2006	09/02/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Allard, M

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